

## New Methods

# Color M-Mode Doppler Flow Propagation Velocity is a Preload Insensitive Index of Left Ventricular Relaxation: Animal and Human Validation

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**OBJECTIVES** To determine the effect of preload in color M-mode Doppler flow propagation velocity ( $v_p$ ).

**BACKGROUND** The interpretation of Doppler filling patterns is limited by confounding effects of left ventricular (LV) relaxation and preload. Color M-mode  $v_p$  has been proposed as a new index of LV relaxation.

**METHODS** We studied four dogs before and during inferior caval (IVC) occlusion at five different inotropic stages and 14 patients before and during partial cardiopulmonary bypass. Left ventricular (LV) end-diastolic volumes (LV-EDV), the time constant of isovolumic relaxation ( $\tau$ ), left atrial (LA) pre-A and LV end-diastolic pressures (LV-EDP) were measured. Peak velocity during early filling (E) and  $v_p$  were extracted by digital analysis of color M-mode Doppler images.

**RESULTS** In both animals and humans, LV-EDV and LV-EDP decreased significantly from baseline to IVC occlusion (both  $p < 0.001$ ). Peak early filling (E) velocity decreased in animals from  $56 \pm 21$  to  $42 \pm 17$  cm/s ( $p < 0.001$ ) without change in  $v_p$  (from  $35 \pm 15$  to  $35 \pm 16$ ,  $p = 0.99$ ). Results were similar in humans (from  $69 \pm 15$  to  $53 \pm 22$  cm/s,  $p < 0.001$ , and  $37 \pm 12$  to  $34 \pm 16$ ,  $p = 0.30$ ). In both species, there was a strong correlation between LV relaxation ( $\tau$ ) and  $v_p$  ( $r = 0.78$ ,  $p < 0.001$ ,  $r = 0.86$ ,  $p < 0.001$ ).

**CONCLUSIONS** Our results indicate that color M-mode Doppler  $v_p$  is not affected by preload alterations and confirms that LV relaxation is its main physiologic determinant in both animals during varying lusitropic conditions and in humans with heart disease. (J Am Coll Cardiol 2000;35:201-8) © 1999 by the American College of Cardiology

Doppler echocardiography is the most commonly used diagnostic modality for assessing diastolic function. Indexes derived from transmitral or pulmonary venous Doppler flows are used to characterize patterns of impaired diastolic filling in patients with heart disease (1,2). One of the most important physiologic parameters that allows left ventricular (LV) filling at relatively low pressure is the rate of relaxation. Best defined by the time constant of isovolumic pressure decay ( $\tau$ ), LV relaxation is an important determinant of early transmitral pressure gradients which in turn determine transmitral Doppler filling patterns. Thus, im-

paired relaxation has been shown to decrease peak early filling velocity (E) and increase peak rate of atrial filling (A) in patients with LV hypertrophy, early restrictive cardiomyopathy and during ischemia (2-4). However, experimental and clinical studies have also shown a compensatory increase in preload results in opposite effects on these Doppler indexes (5,6), causing "pseudonormalization" of the LV filling pattern (7).

The propagation velocity of early flow into the LV cavity ( $v_p$ ) measured by color M-mode Doppler was first proposed by Brun et al. (8) as an index of left ventricular relaxation. Animal and human studies have since confirmed that  $v_p$  is closely related to  $\tau$  (9,10). In addition, earlier animal studies indicated that  $v_p$  was relatively insensitive to small alterations in left atrium (LA) pressure and heart rate (9).

The objectives of the following study were: 1) to evaluate the influence of preload on E and  $v_p$  measured by color M-mode, and 2) to determine the relationship between these Doppler indexes and physiologic parameters of sys-

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#### Abbreviations and Acronyms

A	= peak atrial contraction velocity
E	= peak early transmitral flow velocity
IVC	= inferior vena cava
LA	= left atrium
LV	= left ventricle or ventricular
LV-EDP	= left ventricular end-diastolic pressure
LV-EDV	= left ventricular end-diastolic volume
LV-EF	= left ventricular ejection fraction
LV-ESP	= left ventricular end-systolic pressure
LV-ESV	= left ventricular end-systolic volume
tau	= time constant of isovolumic relaxation
TD	= time delay
TEE	= transesophageal echocardiography
$v_p$	= color M-mode flow propagation velocity

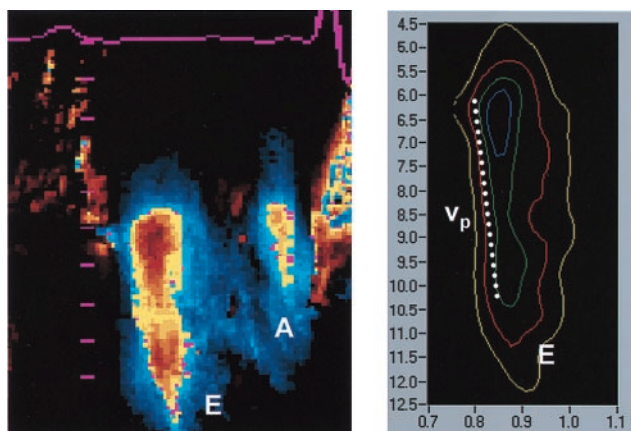
tolic and diastolic function in healthy animals during varying lusitropic conditions and in humans with cardiac disease.

## METHODS

**Animal study.** Four healthy mongrel dogs weighting  $27.5 \pm 0.4$  kg (range 26.5 to 29 kg) were anesthetized with sodium pentobarbital (30 mg/kg IV for induction, 1.0 mg/kg/h for maintenance) and ventilated with room air by a Mark 7 Respirator (Bird Products, Palm Springs, California). The protocol was approved by the Institutional Animal Care and Research Committee and conformed to the position of the American Heart Association on research animal use. The right femoral and carotid arteries and the right internal jugular vein were isolated and cannulated with valve sheaths (USCI, Billerica, Massachusetts; Hemaquet 8F). A 6 Fr 11-pole combination multielectrode conductance catheter with dual high-fidelity pressure sensors (Millar Instruments, Houston, Texas) was advanced after adequate calibration from the right carotid artery to the LV apex using echocardiographic guidance. The electrical impedance measured by five pairs of conductance electrodes was analyzed by a conductance data processor (Leycom Sigma 5DF, Leyden, Netherlands) as previously described (11). The pressure transducers were positioned in the LV cavity and the proximal ascending aorta. A 23-mm Mansfield balloon catheter (Boston Scientific, Maple Grove, Minnesota) was introduced through the femoral vein and advanced to the upper limit of the inferior vena cava (IVC) under fluoroscopic guidance. The balloon catheter was inflated intermittently throughout the experiment to occlude caval flow. Arterial blood pressure and central venous pressure were monitored via fluid-filled catheters together with a single ECG lead coupled to an oscilloscopic multichannel recorder (EM models M1101C and M2101B, Honeywell, Pleasantville, New York). Two-dimensional and Doppler echocardiographic studies were performed with an Acuson Sequoia (Mountain View, California) ultrasound machine using a multifrequency transducer

(Model 3V2c). From the apical four-chamber view, pulsed Doppler recordings of the LV inflow were acquired. From the same echocardiographic window, the color Doppler map of the mitral inflow was displayed, and M-mode recordings were acquired after aligning the cursor in the direction of the inflow jet. Pulsed and color M-mode Doppler were recorded at a horizontal sweep speed of 100 mm/s and stored digitally. A timing signal marker was coupled to the echocardiographic system and to the data acquisition board in order to match pressure, volume and Doppler signals for each corresponding heart beat. Left ventricular volume and pressure, ECG and timing marker signals were digitally acquired with 1 ms resolution using a multifunction I/O (input/output) board (AT-MIO-16, National Instruments, Austin, Texas) interfaced with a computer workstation (Pentium 200 MHz PC, Gateway, Sioux Falls, North Dakota) using customized software developed using LabVIEW v. 5.0 (National Instruments, Austin, Texas). From the LV pressure waveform, the time constant of isovolumic relaxation (tau) was determined using Weiss' (12) monoexponential equation ( $P = P_0 \times e^{-t/\tau}$ ; whereas P is LV pressure at time t,  $P_0$  is LV pressure at peak negative dP/dt and t is time after negative dP/dt) and after curve fitting by use of the Levenberg-Marquardt nonlinear least-squares parameter estimation technique (13). A basic assumption of a zero-asymptote was adopted as suggested by Yellin et al. (14).

A total of five different inotropic-lusitropic conditions were available in each animal including 1) baseline, 2) dobutamine at 5  $\mu\text{g/kg/min}$ , 3) dobutamine at 10  $\mu\text{g/kg/min}$ , 4) esmolol at 50  $\mu\text{g/kg/min}$ , and 5) esmolol at 100  $\mu\text{g/kg/min}$ . A period of stabilization was allowed between each stage (range 3 to 20 min). All animals received 1,000 ml of Ringer's lactate before the initiation of the experiment. Volume and pressure data were collected continuously before and during caval occlusion. Color M-mode Doppler images were acquired immediately before and 5–10 seconds after each occlusion. From color M-mode Doppler images, the magnitude and location of velocities were determined at each color pixel. The position and magnitude of maximal velocity in the early filling waveform was automatically located (Fig. 1). Pixels containing velocity magnitudes corresponding to 25%, 50% and 75% of the maximal velocity were connected creating several isovelocity contour lines. Flow propagation velocity ( $v_p$ ) was measured as the slope of the first 50% isovelocity contour line. In order to analyze  $v_p$  and early filling (E) simultaneously from the same heart beats, E and atrial contraction (A) velocity components were extracted at mitral leaflet tips from the color M-mode Doppler data. In order to validate the accuracy of peak component E and A velocities derived by digital analysis from color M-mode Doppler images, these were compared against pulsed Doppler velocities obtained sequentially during each stage in the human experiments. The correlation between both methods was excellent ( $r = 0.97$ ,  $y = 0.91x + 2.5$  cm/s,  $p < 0.001$ , SEE = 5.7 cm/s,



**Figure 1.** Automated method of determining flow propagation velocity ( $v_p$ ). A color M-mode Doppler image obtained by transesophageal echocardiography is shown at the left. The value of each color pixel is decoded. The maximum velocity value obtained during early filling (E) is detected. Isovelocity lines connecting pixels that encode values of 25% (yellow line), 50% (red line), 75% (green line) and 100% (blue line) of the maximum value are displayed in the right panel. The slope of the 50% isovelocity line is then determined. See text for details.

$\Delta = 2.9 \pm 6.0$  cm/s). In those cases when separation of E and A waves was not possible ( $n = 7$ , 35%) we measured  $v_p$  as the slope of the single wavefront and E as the peak velocity of the single filling wave. Intra- and interobserver variability of  $v_p$  measurements were 8% and 12%, respectively ( $r = 0.95$ ,  $p < 0.001$ ).

**Human study.** We studied 14 patients (age  $64 \pm 11$  years, 11 men) undergoing open-heart surgery (coronary artery bypass = 9, mitral valve = 2, aortic valve = 1, combined = 2). All patients provided informed consent and were hemodynamically stable and in regular sinus rhythm at the time of the study. The institutional review board of the Cleveland Clinic Foundation approved the protocol. All patients underwent a complete transesophageal echocardiographic (TEE) study using a Hewlett-Packard Sonos 1500 or 2500 (Andover, Massachusetts) equipped with a multiplane transesophageal probe. After the pericardium was opened and major cardiac vessels cannulated, calibrated dual-sensor high fidelity pressure transducer catheters (Millar, Inc., Houston, Texas, Model SPC-751) were introduced through the right upper pulmonary vein and advanced under TEE guidance until the distal transducer was in the LV and the proximal in the LA. Two-dimensional images of the LV were acquired from TEE four- and two-chamber views, and volumes were calculated using Simpson's rule. Pulsed and color M-mode Doppler recordings were also acquired and stored as described for the animal experiment. In addition, the audio Doppler signals (forward and reverse flow) were directly acquired at 20 kHz using a sound multifunction I/O board (National Instruments, Austin, Texas). These were processed using a short-time Fourier transform to reconstruct spectral Doppler images with 5 ms resolution. Ex-

tracted Doppler velocity profiles were resampled to allow precise temporal alignment of pulsed Doppler and LV and LA pressure data. Color M-mode images were aligned by means of a timing signal marker. Two complete sets of data including echocardiographic LV volumes, LA and LV pressures, pulsed and color M-mode Doppler were acquired during suspended ventilation before and during partial (1.5 to 2 L/min) cardiopulmonary bypass.

**Data analysis.** Statistical analysis was performed using commercially available software (Sigmastat version 6.0). In the animal study, peak E and A velocities, E/A ratio, color M-mode Doppler  $v_p$ , LV end-diastolic (LV-EDV), end-systolic (LV-ESV) volumes, ejection fraction (LV-EF), end-systolic (LV-ESP) and end-diastolic (LV-EDP) pressures and tau were compared between baseline, peak dobutamine stimulation and maximum esmolol dose using one-way ANOVA for repeated measurements with Dunnett's test for post-hoc analysis. The same indexes were also compared before and during IVC occlusion in dogs and before and during partial bypass in humans using Student  $t$  test for paired data. The association between  $v_p$  and other variables was tested using simple and multiple linear regression in both dogs and humans. Statistical significance was defined as  $p < 0.05$ . Data are expressed as mean  $\pm$  standard deviation.

To test the hypothesis that  $v_p$  is independent of preload,  $v_p$  was compared pre- and post-preload reduction. The effect of preload reduction on E and  $v_p$  was compared by paired t-testing. A  $p < 0.05$  was taken as evidence that  $v_p$  is less preload dependent than E.

To test the hypothesis that  $v_p$  is an index of LV relaxation (tau), linear and nonlinear regression using test functions such as polynomial, power and exponential were used to determine the optimal function relating these variables. To test whether these relations were similar for both the canine and human data, one-way analysis of covariance was used, where tau was the independent variable,  $v_p$  was the covariate, and canine versus human was the discrete variable.

## RESULTS

**Animal study.** Baseline LV-ESP and LV-EF increased at peak dobutamine dose volume and decreased with maximum dose of esmolol. Left ventricular end-diastolic pressure decreased with dobutamine and increased with esmolol. Changes in lusitropy were also induced with tau decreasing with dobutamine and increasing with esmolol. Other parameters are shown in Table 1. Figure 2 is a representative example of color M-mode recording of the LV inflow obtained at baseline and during dobutamine and esmolol infusion. Color M-mode  $v_p$  increased from baseline to dobutamine and decreased with esmolol.

**Effects of preload alteration.** Left ventricular end-diastolic volume and LV-EDP decreased from baseline to IVC occlusion. There was a small but not clinically relevant decrease in tau (from  $62 \pm 31$  to  $56 \pm 31$  ms,  $p < 0.001$ ).



**Table 1.** Animal Study: Effects of Inotropic Modulation

	Baseline	Esmolol	Dobutamine	p
LV-EDV (ml)	58.1 ± 12.2	66.2 ± 42.2	33.9 ± 13.0	0.21
LV-ESV (ml)	26.0 ± 2.9	35.2 ± 24.0	12.0 ± 9.3	0.19
LV-EF	0.54 ± 0.07	0.47 ± 0.12	0.66 ± 0.13	0.11
LV-ESP (mm Hg)	118 ± 24	104 ± 31	141 ± 20	0.12
LV-EDP (mm Hg)	8.9 ± 3.8	15.3 ± 3.3*	8.7 ± 2.4	< 0.001
HR (beats/min)	84 ± 21	86 ± 15	117 ± 30*	0.005
tau (ms)	59 ± 23	93 ± 46*	39 ± 15	0.05
E (cm/s)	55 ± 15	50 ± 25	64 ± 24	0.19
A (cm/s)	48 ± 21	45 ± 12	46 ± 10	0.84
v <sub>p</sub> (cm/s)	37 ± 13	22 ± 9*	49 ± 20*	< 0.001

\*Statistically different from baseline.

LV-EDV = left ventricular end-diastolic volume; LV-ESV = left ventricular end-systolic volume; LV-ESP = left ventricular end-systolic pressure; LV-EDP = left ventricular end-diastolic pressure; LV peak (-) dP/dt = left ventricular peak time derivative of pressure decay; tau = time constant of isovolumic relaxation; E = peak early filling velocity; A = peak atrial contraction velocity; v<sub>p</sub> = color M-mode flow propagation velocity.

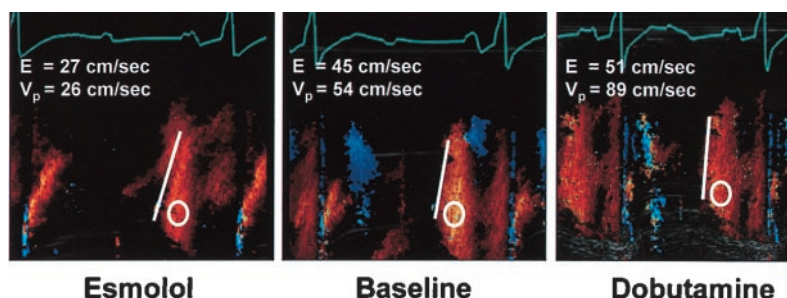
Figure 3 is a representative example of a color M-mode recording of the LV inflow obtained before and during IVC occlusion. The change in the color velocity map (yellow to red) indicates lower component (E and A) velocities. However, the slope of the wavefront of early filling (v<sub>p</sub>) is unchanged. Peak Doppler E velocity decreased from 56 ± 21 to 42 ± 17 cm/s after IVC occlusion (p < 0.001) with a smaller decrease in peak A velocity (from 45 ± 12 to 38 ± 12 cm/s, p = 0.003). In contrast to peak E velocities, v<sub>p</sub> did not decrease during caval occlusion in the animals (from 35 ± 15 to 35 ± 16, p = 0.99), confirming the preload independence of this index (Fig. 4). Overall, E showed a 14.2 ± 10.4 cm/s decrease with preload reduction in contrast to v<sub>p</sub> which showed no significant change (0.0 ± 3.6 cm/s, p < 0.0001, Table 2).

**Physiologic determinants of v<sub>p</sub>.** By univariate analysis, color M-mode Doppler v<sub>p</sub> showed a statistically significant negative correlation against tau (r = -0.65, p < 0.001) and LA pressure (r = -0.65, p < 0.001) and a positive correlation against LV-EF (r = 0.54, p < 0.001), LV-ESP (r = 0.43, p = 0.004) and heart rate (r = 0.82, p < 0.001). By multivariate analysis only tau (p < 0.001), heart rate (p < 0.001) and LV-EF (p = 0.03) were independent

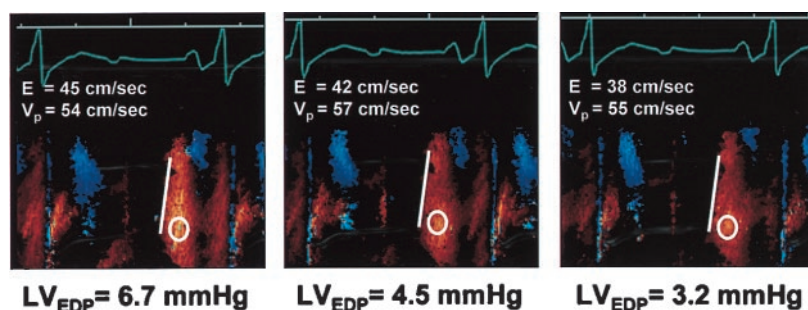
determinants of v<sub>p</sub>. The relation between tau and v<sub>p</sub> was best described by a power function where tau = 775.63(v<sub>p</sub>)<sup>-0.7718</sup> (r = 0.78, p < 0.001).

**Human study.** Left ventricular end-diastolic volume decreased from 92.5 ± 37.4 ml before cardiopulmonary bypass to 78.1 ± 43.9 ml during partial cardiopulmonary bypass (p < 0.001) while mean LA pressure decreased from 15.1 ± 6.2 to 10.3 ± 6.1 mm Hg (p < 0.001). There was no significant change in LV relaxation (tau = 58 ± 16 before vs. 63 ± 25 ms during partial bypass, p = 0.28). Peak Doppler E velocity decreased from 69 ± 15 to 53 ± 22 cm/s (p < 0.001) with no significant change observed in peak A velocity. As in the animal experiments, v<sub>p</sub> did not decrease during preload reduction (from 37 ± 12 to 34 ± 16 cm/s, p = 0.30), confirming also the preload independence of this index in humans (Fig. 5). Overall, E showed a 17.4 ± 16.4 cm/s decrease with preload reduction compared with v<sub>p</sub> (2.8 ± 9.7 cm/s, p < 0.0001, Table 3).

**Physiologic determinants of v<sub>p</sub>.** By univariate linear regression analysis, color M-mode Doppler v<sub>p</sub> showed a statistically significant negative correlation against tau (r = -0.75, p < 0.001) and a positive correlation against LV-EDV (r =



**Figure 2.** Color M-mode Doppler of left ventricular filling obtained during esmolol, at baseline and during dobutamine infusion showing the changes in E and v<sub>p</sub>. Peak E is given by the maximum color encoded velocity value during early filling (inside enclosed circle), while v<sub>p</sub> is given by the slope of the isovelocity lines (white line). E = peak early transmitral flow velocity; v<sub>p</sub> = flow propagation velocity. See text for details.



**Figure 3.** Color M-mode Doppler of left ventricular filling obtained before (**first image**) and during caval occlusion (**second and third images**). Peak early filling component velocity decreases together with left ventricular end-diastolic pressure (LV-EDP), as demonstrated by the changes in pixel colors from yellow to red. In contrast the slope of the early filling wavefront which determines flow propagation velocity ( $v_p$ ) is unchanged. See text for details. LV-EDP = left ventricular end-diastolic pressure;  $v_p$  = flow propagation velocity.

0.44,  $p = 0.02$ ) and ejection fraction ( $r = 0.43$ ,  $p = 0.03$ ). Multivariate regression analysis indicated that only tau was an independent determinant of  $v_p$  ( $p < 0.001$ ). The relation between tau and  $v_p$  was also best described in humans by a power function where  $\tau = 371.79(v_p)^{-0.5019}$  ( $r = 0.86$ ,  $p < 0.001$ ). Analysis of covariance confirmed no significant difference between the canine and human datasets relating  $v_p$  and tau (F ratio = 0.962, adjusted least-squares for dogs:  $34.8 \pm 1.7$  cm/s vs. humans:  $34.7 \pm 2.1$  cm/s,  $p < 0.001$ , Fig. 6).

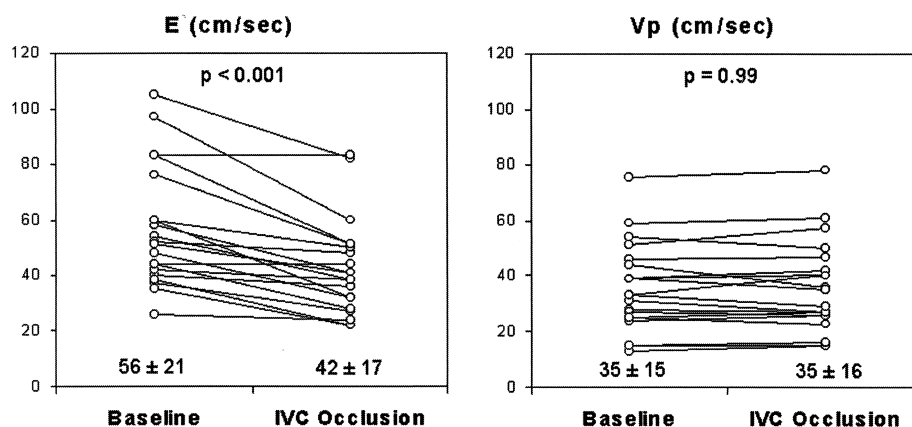
## DISCUSSION

The results of this study indicate that color M-mode Doppler  $v_p$  is not affected by preload alterations in both animals during varying lusitropic conditions and in humans with various types of heart disease. In addition, our findings confirm previously published results (8,9) indicating that LV relaxation is the main physiologic determinant of this diastolic index.

Several studies have related specific Doppler LV filling patterns to diastolic function abnormalities in patients with heart disease (1-4). Older patients and those with hyper-

tensive heart disease and early restrictive cardiomyopathy in whom LV relaxation is impaired, typically present with decreased transmitral E velocity and E/A (early-to-atrial filling) ratio as well as increased pulmonary venous systolic flow. The opposite changes occur when LV relaxation is enhanced during catecholamine stimulation, as shown in our animal experiment (Table 1). At the same time, increasing LV filling pressure results in a linear increase in peak E velocity (5,6,15). Therefore, in patients with advanced diastolic dysfunction, the compensatory or overcompensatory elevation in LA pressure that occurs in order to maintain an adequate cardiac output opposes the effects produced by impaired relaxation causing pseudonormalization of the transmitral filling pattern. This dual dependency limits the utility of conventional Doppler indexes frequently leading to an incorrect diagnosis.

Color M-mode Doppler differs from spectral pulsed Doppler in that it allows the acquisition of spatial information in addition to velocity and time. Earlier studies using color M-mode Doppler have found that in patients with dilated cardiomyopathy the wavefront of early ventricular filling reaches the apex much later than in patients with



**Figure 4.** Animal study: effect of preload reduction in E and color M-mode  $v_p$  IVC occlusion. E = peak early transmitral flow velocity; IVC = inferior vena cava;  $v_p$  = flow propagation velocity.

**Table 2.** Animal Study: Effects of Preload Alterations

	Baseline	IVC Occlusion	p
LV-EDV (ml)	53.8 ± 24.9	43.3 ± 16.4	< 0.001
LV-ESV (ml)	25.9 ± 14.1	20.8 ± 12.2	< 0.001
LV-EF	0.53 ± 0.11	0.54 ± 0.17	< 0.001
LV-ESP (mm Hg)	125 ± 29	103 ± 21	< 0.001
LV-EDP (mm Hg)	10.8 ± 3.8	6.7 ± 3.5	< 0.001
HR (beats/min)	91 ± 23	90 ± 22	0.48
tau (ms)	62 ± 31	56 ± 31	< 0.001
E (cm/s)	56 ± 21	42 ± 17	< 0.001
A (cm/s)	45 ± 12	38 ± 12	0.003
v <sub>p</sub> (cm/s)	35 ± 15	35 ± 16	0.99

Abbreviations same as in Table 1.

normal LV function (16). Previous investigators have measured the delay in apical filling as the slope of the color wavefront (v<sub>p</sub>) or the time delay (TD) for the wavefront to pass from the mitral annulus to the LV apex (8,9). Previous experimental and clinical studies have demonstrated that color M-mode Doppler indexes of LV filling are related to LV relaxation and systolic function (8-10). In normal subjects, v<sub>p</sub> has been reported between 55 and 100 cm/s (8,17).

The relation between LV relaxation and v<sub>p</sub> may be explained by the presence of regional pressure gradients within the LV cavity. Courtois et al. (18) initially reported the presence of intraventricular gradients in the normal LV, showing consistent apex-to-base gradients in pressure during early filling. Intraventricular pressure gradients are responsible for the mechanism of suction in ventricles with normal relaxation, allowing adequate LV filling and cardiac output even at near-zero LA pressure. Falsetti et al. (19) later demonstrated in a canine model that these gradients increase with isoproterenol and decrease with propranolol. Through Euler's hydrodynamic equation:

$$\frac{\partial p}{\partial s} = -\rho \left[ \frac{\partial v}{\partial t} + v \frac{\partial v}{\partial s} \right]$$

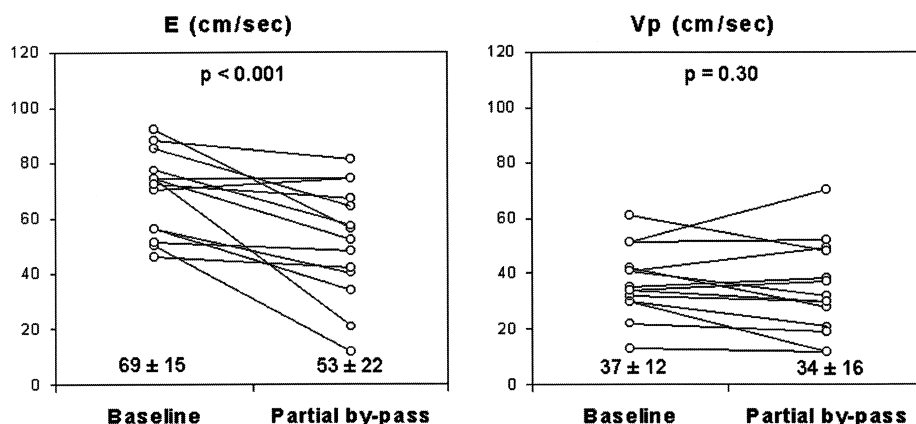
(whereas p = pressure, s = space, t = time and v = velocity), pressure gradients may be related to color M-mode Doppler spatiotemporal velocity distribution providing a physical foundation for the relationship between LV relaxation and v<sub>p</sub> (20).

Several studies have previously shown that tau is not affected by modest changes in loading conditions when heart rate is maintained constant (21,22) and when the decrease in preload is not profound enough to cause alterations in afterload. Although in our animal experiment there was a small decrease in tau suggesting improvement in relaxation, the difference was of no clinical significance. In previously reported animal experiments, volume loading and caval constriction caused only minor, nonstatistical changes in v<sub>p</sub>, suggesting that this index was relatively independent of preload (9). In these previous studies, however, the magnitude of volume change obtained during caval occlusion resulted only in a modest decrease in LA pressure and

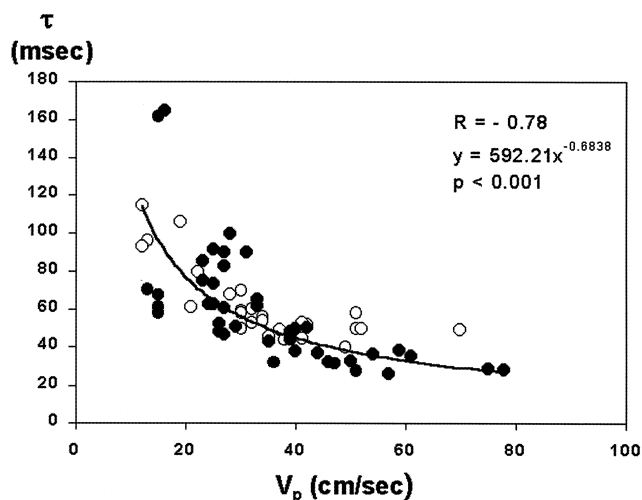
**Table 3.** Human Study: Effects of Preload Alterations Before and During Partial Cardiopulmonary Bypass

	Baseline	Partial Bypass	p
LV-EDV (ml)	92.5 ± 37.4	78.1 ± 43.9	< 0.001
LV-ESV (ml)	41.4 ± 21.1	35.4 ± 19.6	0.004
LV-EF	0.57 ± 0.10	0.54 ± 0.09	0.26
LV-ESP (mm Hg)	100 ± 20	92 ± 18	0.28
mean LAp (mm Hg)	15.1 ± 6.2	10.3 ± 6.1	< 0.001
HR (beats/min)	76 ± 15	76 ± 18	0.95
tau (ms)	58 ± 16	63 ± 25	0.28
E (cm/s)	69 ± 15	53 ± 22	< 0.001
A (cm/s)	59 ± 21	55 ± 27	0.58
v <sub>p</sub> (cm/s)	37 ± 12	34 ± 16	0.30

Abbreviations as in Table 1.



**Figure 5.** Human study: effect of preload reduction in E and color M-mode v<sub>p</sub> during partial circulatory bypass. E = peak early transmitral flow velocity; v<sub>p</sub> = flow propagation velocity.



**Figure 6.** Correlation between flow propagation velocity ( $v_p$ ) and the tau in the combined animal (solid circles) and human (open circles) group (trendline fitted to a power function). tau = time constant of isovolumetric relaxation;  $v_p$  = flow propagation velocity.  $R = -0.78$ ;  $y = 592.21x^{-0.6838}$ ;  $p < 0.001$ .

was not sufficient to cause a statistically significant change in LV-EDP. Volume loading, on the other hand, resulted in a 50% prolongation of TD (not statistically significant). These results may be attributed to the confounding effect of other hemodynamic changes occurring during the longer interval required for volume infusion, as suggested by the observed 40% increase in heart rate. In our animal model, we performed IVC occlusions after volume loading in order to obtain larger alterations in preload. By using a closed-chest model, we avoided hemodynamic perturbations that may be caused by blood loss and lack of pericardial constraint. In addition, we collected our data earlier during IVC occlusion to minimize the effect of compensatory increases in sympathetic tone, as demonstrated by the lack of significant increase in heart rate.

We, as well as other investigators, previously suggested that  $v_p$  was a preload independent index in humans (17,23), based on indirect evidence (lack of correlation between  $v_p$  and LV-EDP in groups of patients with heart disease). However, confounding variables could have accounted for the lack of correlation observed in these previous studies. In this study, preload alterations were caused while carefully avoiding other hemodynamic alterations in our controlled experimental setting.

In this study, a semiautomatic method was implemented in order to objectively measure  $v_p$ , consisting of identifying multiple isovelocity lines within the wavefront of LV filling. We chose arbitrarily the line that connected points where velocity was 50% of the maximum, since this was easily identifiable in all cases. If digital velocity output is available from the ultrasound machine, this semiautomatic method is easily implemented and helps to reduce operator bias compared with the previously reported manual methods.

*Differences between animal and human results.* Although the effects of preload were similar, the relation between  $v_p$  and other parameters was different in both species. These differences may be attributed to different experimental settings (open vs. closed pericardium, IVC occlusion vs. partial circulatory bypass, inotropic modulation in the dogs but not the patients) but are most likely related to underlying pathophysiological differences among both groups (healthy dogs vs. humans with cardiac disease). The association between end-diastolic volume and  $v_p$  observed in humans may reflect a high prevalence of LV hypertrophy and coronary artery disease without impaired systolic function since these tend to have impaired relaxation and small LV cavity. This relation would be different, however, if more patients with dilated LV and low ejection fraction were included in this study.

Our study showed a remarkably low correlation between pulsed mitral Doppler E and tau. This finding likely reflects the effect of pseudonormalization caused by increased LA pressure in some patients. On the other hand, the lack of association between LV-EDP and E in dogs could be attributed to the effect of a concomitant change in LV relaxation that was induced by pharmacological maneuvers. This would also explain the negative correlation observed between LV-EDP and  $v_p$ . The association between E,  $v_p$  and heart rate in the animal study most likely reflect differences in inotropic conditions induced by dobutamine and esmolol and not a direct effect of heart rate changes. This is supported by Stugaard's (9) study in which changes in heart rate during atrial pacing failed to show similar association.

**Study limitations.** In this study we determined component E and A velocities from color M-mode Doppler digital analysis. Such approach was necessary in order to compare the effect of preload on both E and  $v_p$  in the same heart beat and under the same physiologic conditions. In addition, this method allowed obtaining component velocities at the sample depth at the level of the mitral leaflet tips. We validated the accuracy of color M-mode Doppler against pulsed Doppler component velocities in the human study where similar hemodynamic conditions were maintained during independent acquisition of color M-mode and pulsed Doppler recordings.

In animals, separation of E and A waves was not possible in 7 of the 20 (35%) available animal conditions. In such cases, we measured  $v_p$  as the slope of the single wavefront and E as the peak velocity of the single filling wave. The results of preload alterations were similar, however, when we analyzed the cases with distinct E and A waves separately.

Finally, the accuracy of TEE determined LV volumes may be limited. Although we paid careful attention in order to avoid LV foreshortening during these studies, LV volumes may have been underestimated. This underestimation should have affected volumes obtained at high and low



preload in a similar manner, and, therefore, the magnitude of change should still be accurate.

**Conclusions.** Color M-mode Doppler  $v_p$  may be easily obtained with modern ultrasound systems during a routine echocardiographic examination. This index can be useful in the routine clinical evaluation of diastolic function as it provides a preload independent estimate of LV relaxation. For example,  $v_p$  may be used to differentiate patients with normal from those with "pseudonormal" filling (17) and to estimate the effect of LV filling pressure when combined with pulsed Doppler indexes (23). Therefore, color M-mode  $v_p$  should be incorporated into the routine echocardiographic assessment of diastolic function.

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